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Melanoma in Childhood and Adolescence: Clinical and Pathologic Features of 43 Cases

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21

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Melanoma in Childhood and Adolescence: Clinical and Pathologic Features of 43 Cases

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Running Head: Melanoma in Childhood and Adolescence

Abstract

Forty-three cases of melanoma occurring before age 20 years were reviewed from a twenty-one year period at a single center. Thirteen of the patients were preadolescent children, and 90% were Caucasian. Histologic review of 39 available primary tumors showed superficial spreading and nodular types only. Thickness ranged from 0.23 mm to 5.43 mm, with a mean of 1.58 mm. Ulceration was present in 8%, necrosis in 28%, evidence of regression in 21%, and antecedent nevus in 33% of cases. The overall 5 year survival is 79%, with a median follow-up of 42 months. There is no detectable survival difference between preadolescent children and adolescents. Several treatment failures occurred after improper biopsy and/or inaccurate original diagnosis of Spitz's nevus. Of 34 Stage I and II patients given definitive surgical treatment by the authors, the 5 year survival is 95%. Although histologic confusion with Spitz's nevi occasionally occurs, melanoma in this age group can be treated with good results.

Key Words: Melanoma

Childhood, Pediatric

Histologic, Pathologic

Introduction

Melanoma is a rare malignancy in younger age groups, particularly in preadolescent children. Known risk factors include giant hairy nevus, family history of melanoma, xeroderma pigmentosum, and placental transmission(1). Diagnosis is often difficult or delayed, due to certain histologic similarities to epithelioid and spindle cell nevus (Spitz's nevus). The purpose of this report is to examine the clinical and pathologic features of melanoma in 43 young patients seen in one center over the past 21 years.

Methods

Criteria for inclusion into this study included: age less than twenty years at diagnosis; presence of melanoma confirmed by histologic examination of primary lesions (39 cases) or metastatic lesions (4 cases); treatment and follow-up provided by the Division of Surgical Oncology, University of Illinois at Chicago (UIC) between January, 1969 and April, 1990. A total of 43 out of 1,570 (2.7%) melanoma patients seen over that twenty-one year period were eligible for review.

All slides of the primary tumor were reviewed by one dermatopathologist (S.G.R.). The histologic classification used was that proposed by Clark, et al.(2). The thickness was determined according to Breslow(3) and level of invasion according to Clark(2). Other parameters studied were cell type (epithelioid, spindle, nevoid, giant)(2), microscopic ulceration(4), mitosis per mm^2, lymphatic/vascular invasion, antecedent nevus, necrosis, histologic grade, lymphocytic response, and regression. The lymphocytic infiltrate was graded from 0-3 (0 = none; 1 = mild; 2 = moderate; 3 = well developed), and its location was noted (i.e., whether it was at the base or within the tumor or both). The criteria for regression used was that described by McGovern, et al.(5) and modified by Ronan, et al.(6). The extent of regression was determined in percent(6). Histologic grading was done based on cytologic atypia (grade 1 = mild; 2 = moderate; 3 = marked atypia). The type of antecedent nevus present was further classified as to whether or not it showed dysplasia or had features of a congenital nevus(7). The mitotic rate was determined with the use of an ocular micrometer disc grid in the area with the highest mitotic activity.

Of the 43 patients, 8 were initially treated outside; 6 of these had recurrent disease at the time of referral to our institution. Thirty-four patients (79%) had definitive surgical treatment at our institution as follows: 24 patients underwent wide excision, 10 patients had wide excision with regional node dissection (9 elective, 1 therapeutic). One patient presented with brain metastases and underwent craniotomy only. Those patients with recurrent disease were treated with reoperation, irradiation, systemic chemotherapy, regional limb perfusion, immunotherapy and/or hormonal therapy as appropriate.

All patients were followed at no more than 12 month intervals in the Surgical Oncology Clinic at UIC. Data were entered into a computerized melanoma registry. Survival distribution was estimated using the product limit method of Kaplan and Meier(8).

Results

The age distribution in this series is depicted in Figure 1, which shows a general increase in incidence of melanoma with age, particularly after puberty. All but four patients were Caucasian, despite the large non-white population in the Chicago area. The clinical data on these 43 patients is summarized in Table 1. Four of the thirteen preadolescent children had an associated risk factor, including three patients (23%) with a family history of melanoma and an 8-year-old girl with a giant hairy nevus of the trunk and extremities. One 10-year-old white boy with albinism had a nodular melanoma, as seen in Figures 2a and 2b. There were no cases of congenital melanoma or xeroderma pigmentosum in this series.

Three patients were taking exogenous hormones at the time of diagnosis: a 4-year-old boy on thyroxine replacement for congenital hypothyroidism, a 10-year-old girl on estrogen replacement since infancy following a bilateral oophorectomy and hysterectomy for a "congenital malformation" of her reproductive organs, and a 19-year-old girl on oral contraceptives for three years.

The histopathologic characteristics of the primary melanoma of 39 patients are summarized in Table 2. Thickness ranged from 0.23 mm to 5.43 mm, with a mean of 1.58 mm. There were no cases of lentigo maligna or acral lentiginous melanoma. Of the 18 tumors with evidence of an antecedent nevus, 4 had histologic features of congenital nevus as described by Mark, et al.(7). Microscopic ulceration was present in 3 cases (8%), lymphatic or vascular invasion in 2 cases (5%), necrosis in 11 cases (28%), and regression in 8

cases (21%). Epithelioid cells predominated in 35 cases (90%) and spindle cells in 4 cases (10%).

Median follow-up in this series is 42 months, with a range from 1 to 196 months. One patient was lost to follow-up at 96 months. The survival distributions for all patients and for those treated initially by the authors at UIC are shown in Figure 3. Of the latter group, 24 underwent wide excision only and all are alive at 2 to 121 months. Of the 10 patients who underwent lymphadenectomy, 4 were node positive; one died at 27 months (Table 3, patient #8), and the remainder are alive disease-free at the time of this report. One of the node-negative patients recurred in the opposite axilla and is alive with disease at 57 months (Table 3, patient #9).

The overall survival for the 34 UIC patients at 5 years is 95%. For the entire 43 patients under 20 years of age, the overall survival at 5 years is 70% (see Fig. 3). No survival difference was seen in preadolescent versus adolescent patients.

Information regarding the 9 patients who developed recurrence is given in Table 3. Patient #5 had a giant hairy nevus of the trunk and extremities, and developed brain metastases despite treatment by multiple elective skin excisions with grafting. Patient #4 had an initial diagnosis of Spitz's nevus based on the lesion's small size (<5.0 mm), symmetry, predominant spindle cell population, sharp circumscription, and the absence of pagetoid spread, mitosis, and pigmentation. In addition, the cells of the lesion were uniform, with no pleomorphism or hyperchromatism. A national referral center confirmed the diagnosis of Spitz's nevus. The lesion recurred at 7 months, and again this was read as Spitz's nevus. A second local recurrence developed at 15

months, and at 14 years, metastatic melanoma to the regional nodes, lungs, and bone developed (Figures 4a, 4b, and 4c).

Patient #7 was also initially diagnosed as Spitz's nevus by the original pathologists, with confirmation by a national referral center. The tumor was composed of uniform spindle cells that were streaming vertically from the epidermis to the underlying dermis and fat. There was no pagetoid spread and the lesion was well circumscribed. After 18 months, the patient developed metastases to the regional nodes, and later to the brain and lungs.

Discussion

In our center, 3% of melanoma patients were under twenty years of age, and less than 1% were preadolescent. Otherwise, the incidence of melanoma in these age groups was similar to adults, with a roughly equal male/female ratio and 90% Caucasians. Primary tumors were found in all locations in the body, the lower extremity being the most frequent. A similar distribution has been seen in other recent large series(1,9-12).

In the preadolescent group, one-third had a known risk factor for melanoma (i.e., family history of melanoma or giant hairy nevus), suggesting that risk factors may be important in these age groups. The occurrence of melanoma in patients with albinism is quite unusual. These patients have a marked sensitivity to sun exposure and develop many malignant and pre-malignant skin lesions; an increased incidence of melanoma, however, has not been reported(14,15).

Although exogenous hormones, particularly estrogens, have not been conclusively linked to the causation of melanoma, hormone receptors in human tumors have been demonstrated biochemically in some centers(16,17). This series of young patients contains two patients given estrogen and one given thyroxine for several years prior to diagnosis of melanoma.

The pathologic features of melanoma in this age group are different from those in adults in several aspects. Acral lentiginous and lentigo maligna melanoma did not occur in this series. This is in sharp contrast to our experience in patients over 70 years of age, in which acral lentiginous melanoma occurs at a relatively high frequency (16%) and is associated with a poor survival (unpublished results). Lentigo maligna melanoma is known to be

more common in the elderly (Hutchinson's freckle) and carries a favorable prognosis.

Antecedent nevi (5 congenital) were seen in almost half of our young patients. The management of congenital nevi in children is controversial primarily because the true incidence of melanoma in these lesions is unknown. The potential use of estrogen receptor as a marker for the development of melanoma has been suggested by Chaudhuri, et al.(18). It is generally agreed, however, that giant hairy nevi should be excised electively due to the high risk of metastatic melanoma (14% in one review)(19).

The histologic features of melanoma in a predominantly adult population of 1,350 patients seen in our center has also been recently reported(21). In comparison, ulceration was less frequent in young patients (8% vs. 29%), as was tumor regression (18% vs. 48%). The incidence of vascular invasion, however, was similar (5% vs. 6%).

Initial treatment appeared to be an important factor in survival. As seen in Table 3, several treatment failures occurred after improper biopsy and/or misdiagnosis as Spitz's nevus. Patient #3, whose initial lesion was simply fulgurated, illustrates the importance of submitting all skin lesions for pathologic examination. Patients #4 and #7 illustrate the difficulty of differentiating Spitz's nevi from melanoma, even among experienced pathologists. Okun(21) described two patients ages 16 and 14 with histologic features of Spitz's nevi who succumbed to metastatic melanoma at 6 and 1 years, respectively. Similarly, Peters, and Goellner(22), without knowledge of follow-up or previous diagnosis, retrospectively studied the histologic material from 52 patients under 20 years of age who were diagnosed with either

melanoma or Spitz's nevus. Of 33 cases reclassified as Spitz's nevus, 2 had developed metastatic melanoma.

It appears that Spitz's nevi and melanoma have similar features, and no single criterion is reliable in distinguishing the two lesions in young patients. The following features are associated with melanoma: higher degree of pagetoid spread of the tumor into the overlying epidermis, cellular pleomorphism, nuclear hyperchromatism and increased mitotic activity(22). In addition, it has been the experience of one of the authors (S.G.R.) that the following features are associated with Spitz's nevi: infiltration of single cells in the papillary & reticular dermis without disturbance of the spatial arrangement of the collagen bundles or adnexae, absence of an expansile dermal nodule, bland nuclear morphology with thin and delicate nuclear membrane, small nucleoli, uniform chromatin pattern, and few abnormal or bizarre mitotic figures.

Pediatricians and other clinicians should consider melanoma in the differential diagnosis of any suspicious pigmented lesions in young patients, especially those with any of the predisposing conditions mentioned earlier. After biopsy, a correct diagnosis can be made in the majority of cases. The diagnosis of Spitz's nevus should be made only after careful review by experienced pathologists, and wide excision should be considered - particularly if doubt remains about the diagnosis. Our follow-up data indicate that good survival can be achieved with appropriate surgical treatment.

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Table 1
Clinical features of melanoma in 43 patients under twenty years of age.

		No.	(%)
Sex	Male	25	(58)
	Female	18	(42)
Race	White	39	(90)
	Black	2	(5)
	Hispanic	2	(5)
Site	Head and Neck	6	(14)
	Trunk	13	(30)
	Upper extremity	5	(12)
	Lower extremity	17	(40)
	Perineum	1	(2)
	Giant hairy nevus	1	(2)
Associated Conditions	Familial	3	(7)
	Giant hairy nevus	1	(2)
	Albinism	1	(2)
	Hormonal cherapy	3	(7)

Table 2

Table 2. Histologic features of 39 primary melanomas in patients under 20 years of age.

		No.	(%)
Histologic Type	Superficial Spreading	29	(74)
	Nodular	10	(26)
Levels of Invasion	I	0	(0)
	II	14	(36)
	III	7	(18)
	IV	16	(41)
	V	2	(5)
Thickness	<0.75	14	(36)
	0.75 - 1.50	14	(36)
	1.51 - 3.0	7	(18)
	>3.0	4	(10)
Mitotic Rate (per mm^2)	<3	23	(59)
	3 - 6	14	(36)
	>6	2	(5)
Histologic Grade	1	17	(44)
	2	20	(51)
	3	2	(5)
Lymphocytic Infiltration	0	1	(3)
	+	14	(36)
	++	16	(41)
	+++	8	(20)

#	Age	Race	Sex	Site	Level	Depth	Type	Treatment	Recurrence	Treatment	Survival	Comments
1	19	W	M	Upper Back	N/A	N/A	N/A	WE & RND	Local/ Regional	re-excision, CT	2yr	1^+ axillary node; Local/Regional recurrence X 8
2	19	W	M	Neck	N/A	N/A	N/A	WE & RND	Local/ Regional	re-excision, CT, IT	3yr	0^+ axillary nodes; Local/Regional recurrence X 8
3	15	B	F	Eye-brow	N/A	N/A	N/A	Fulguration	1. Parotid 2. Brain, Bone	parotidectomy, CT, IT	2yr	"Hemangioma" treated by fulguration only
4	12	W	F	Thigh	III	0.92	SSM	Local Excision	1,2. Local 3. Regional 4. Lung	re-excision RT, CT, IT	15yr	Originally read as Spitz's nevus, Massive inguinal metastases 14 y later
5	8	H	F	Trunk, Upper & Lower Ext.	-	-	-	Multiple Excision & Grafting	Brain	Craniotomy, RT, CT	4mo	H/O giant hairy nevus; presented with cerebral hemorrhage 2^o metastatic melanoma
6	19	W	F	Foot	V	2.00	SSM	Local Excision	1. Local/Regional 2. Skin	re-excision RND, RT, HT	4yr	H/O bilat. oophorectomy age 1; on estrogen. Local/Regional recurrence X 5
7	13	W	M	Deltoid	V	8.5	NM	Local Excision	1. Local/Regional 2. Lung, Brain	re-excision RND, RT, RLP, CT	3yr	Originally read as Spitz's nevus
8	19	W	M	Deltoid	IV	4.28	NM	WE & RND	Brain, Lung	CT	2yr	1^+ axillary node
9	16	W	M	Upper Back	IV	1.4 with regression	SSM	WE & RND	1. Regional 2. Lung, Kidney	RND, IT	*	0^+ axillary nodes initially; recurred in contralateral axilla

Table 3. Patterns of recurrence in 9 patients. N/A = slides not available. WE = wide excision; RND = regional node dissection; RT = radiation therapy; CT = systemic chemotherapy; IT = immunotherapy; HT = hormonal therapy; RLP = regional limb perfusion; * = alive with disease at 57 mos.

Legends

Figure 1. Age incidence of melanoma in patients under 20 years at diagnosis.

Figure 2a. Nodular melanoma from a 10-year-old boy with cutaneous albinism (H&E, x25). Inset shows epithelioid tumor cells with prominent nucleoli and increased mitotic activity (H&E, x100).

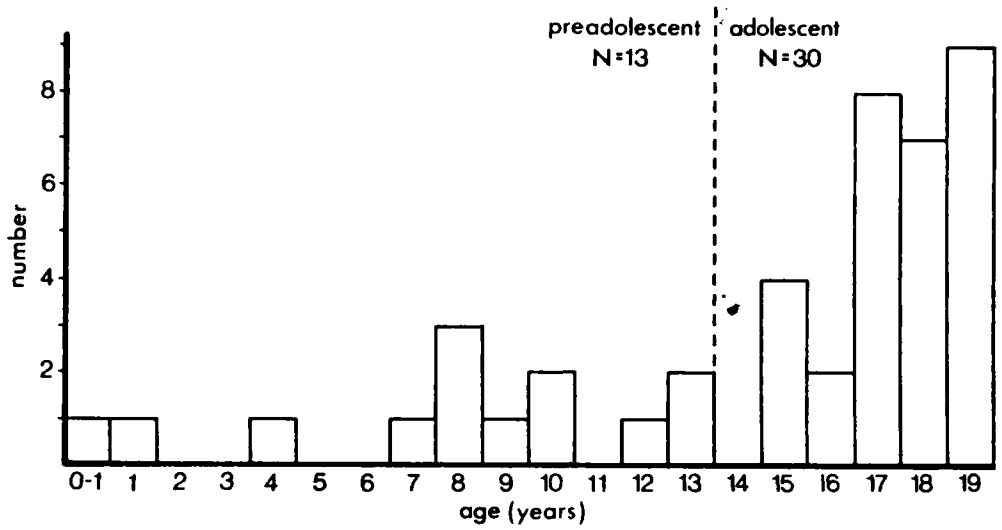
Figure 2b. Metastatic melanoma to superficial inguinal node of same patient (H&E, x100).

Figure 3. Overall survival distribution for all 43 patients under 20 years and for 34 stage I and II patients treated by the authors (UIC).

Figure 4 a. Melanoma from the thigh of a 12-year-old girl (patient #4 in Table 3) initially diagnosed as Spitz's nevus (H&E, x25). Inset shows well-demarcated uniform spindle shaped tumor cells arranged perpendicular to the epidermis (H&E, x100).

Figure 4 b. Recurrent melanoma in same patient one year later showing spindle cells with slight pleomorphism (H&E, x25; inset H&E, x100).

Figure 4 c. Metastatic melanoma of inguinal lymph node in same patient 14 years later. The tumor cells are epithelioid in contrast to the spindle cells of the primary tumor (H&E, x25; inset H&E, x100).


preadolescent
N=13
adolescent
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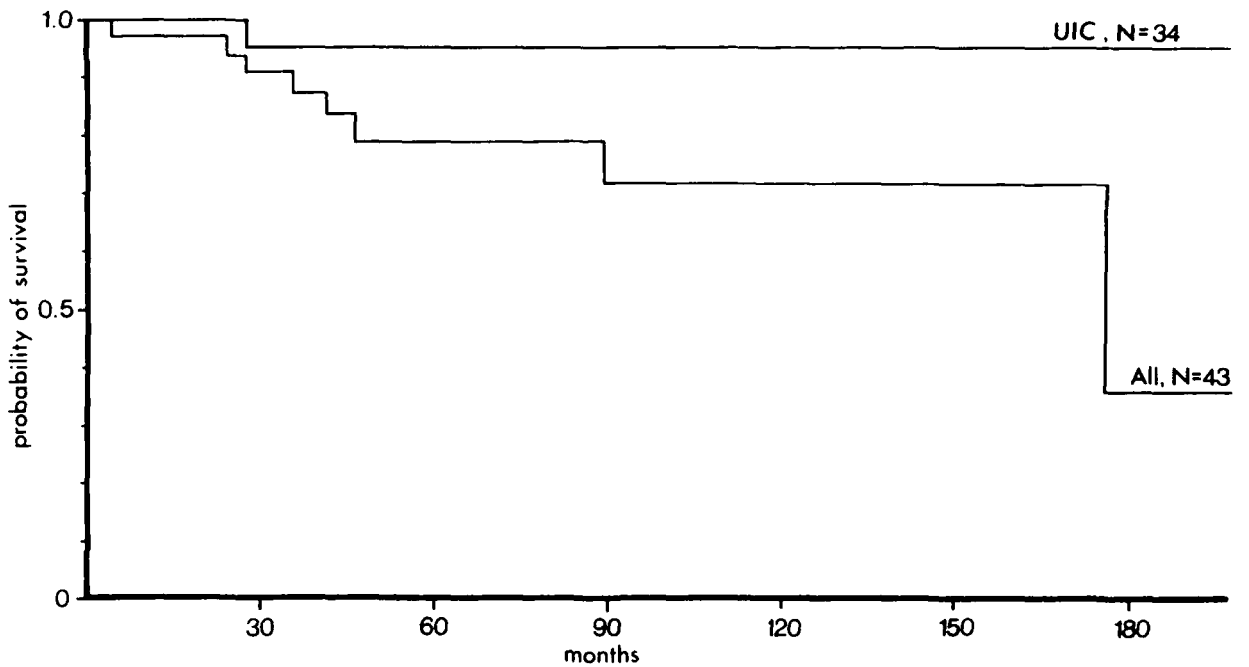
number
8
6
4
2
0-1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
age (years)


1.0
0.5
0
probability of survival
UIC , N=34
All, N=43
30
60
90
120
150
180
months